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D E C I S I O N
of 30 June 2005

Case Number: T 1220/03 - 3.3.2

Application Number: 98929631.4

Publication Number: 0983066

IPC: A61K 31/405

Language of the proceedings: EN

Title of invention:

Pharmaceutical compositions comprising alkanoyl L-carnitine in combination with a statine for treating pathologies brought about by an altered lipid metabolism

Applicant:

SIGMA-TAU Industrie Farmaceutiche Riunite S.p.A.

Opponent:

-

Headword:

Alkanoyl L-carnitine/SIGMA-TAU

Relevant legal provisions:

EPC Art. 56

Rules of Procedure 10b(1)

Keyword:

"Main and first auxiliary request - inventive step (no):
composition of L-carnitine and statin known;
Esterification of L-carnitine obvious"
"Admissibility of second auxiliary request (no): late filed"

Decisions cited:

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Catchword:

-



Case Number: T 1220/03 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 30 June 2005

Appellant: SIGMA-TAU Industrie
Farmaceutiche Riunite S.p.A.
Viale Shakespeare, 47
I-00144 Roma (IT)

Representative: -

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 10 July 2003
refusing European application No. 98929631.4
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
P. Mühlens

Summary of Facts and Submissions

- I. European patent application No. 98 929 631.4 (publication No. WO 99/01126) was refused by a decision of the examining division on the basis of Article 97(1) EPC for lack of inventive step under Article 56 EPC.

Claim 1 of the single request before the examining division reads as follows:

"An orally or parenterally administrable pharmaceutical composition which comprises an alkanoyl L-carnitine wherein the linear or branched alkanoyl group has 2-6 carbon atoms, or one of its pharmacologically acceptable salts, and a statin."

- II. The following documents were cited *inter alia* during the proceedings before the examining division and before the board of appeal:

- (1) DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US, Abstract: SAVICA V ET AL: "The hypotriglyceridemic action of the combination of L-carnitine + simvastatin vs. L-carnitine and vs. simvastatin", XP002081551, CLIN TER, JAN 1992, 140 (1 PT 2)
- (2) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill, New York 1996, p. 1567
- (3) US 4 268 524

III. The examining division considered that the subject-matter of claim 1 having regard to documents (1) and (2) was obvious to a person skilled in the art.

Since, from the state of the art, a synergistic effect of the use of L-carnitine and simvastatin in the treatment of altered lipidemia was known and better results referring to the use of alkanoyl L-carnitine with statins were not claimed in the application as filed, the subject-matter of the application lacked inventive step.

IV. The appellant lodged an appeal against the decision of the examining division.

V. Dated 17 June 2005, a communication was sent out, drawing the appellant's attention to possible problems concerning Articles 84 and 52(4) EPC.

VI. Oral proceedings took place on 30 June 2005. At the oral proceedings, after a thorough discussion and several withdrawn versions of sets of claims, the appellant finally filed new sets of claims as main request and first and second auxiliary requests.

The wording of claim 1 of the **main request** is the same as claim 1 before the examining division.

Claim 1 of the **first auxiliary request** reads:

"An orally or parenterally administrable pharmaceutical composition which comprises propionyl L-carnitine or one of its pharmacologically acceptable salts, and a statin."

The appellant attempted to file a **second auxiliary request** which was not admitted to the proceedings. The wording of its claim 1 is:

"An orally or parenterally administrable pharmaceutical composition which comprises propionyl L-carnitine or one of its pharmacologically acceptable salts, and a dosage of 5 mg/day of a statin."

VII. The arguments of the appellant both in the written procedure and in the oral proceedings may be summarised as follows:

The advantage of the composition as claimed over the state of the art was that a reduction of the dose of statin with respect to routine doses was possible while achieving nevertheless the same anticholesterolaemic and antitriglyceridaemic action, particularly a cholesterolaemia-lowering and triglyceridaemia-lowering effect.

The teaching of (3) referred to a mixture of D- and L-carnitineesters and to an improvement of the high density lipoprotein (HDL) level in serum. In particular, because the skilled person knew about the toxic effects of D-carnitine and its derivatives he would not have taken it into account with respect to the teaching claimed in the application in suit. Nothing in this document suggested using alkanoyl L-carnitines together with statines to lower cholesterolaemia- and triglycerid-levels.

VIII. The representative requested that the decision under appeal be set aside and that a patent be granted on the basis of the main or the first auxiliary request filed in the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.
2. The claims of the main request and the claims of the first auxiliary request are based on claims 1 to 5, 8 and 10 to 11 as originally filed.

With respect to these requests, the requirements of Article 123(2) EPC are consequently satisfied.

3. During the oral proceedings and before trying to file the second auxiliary request, the appellant, even on topics set out in detail in the board's communication, had already extensively used the opportunity to file different sets of claims. These sets of claims did not fully meet the concerns expressed in the communication. After the final main request and first auxiliary request were filed, the new second auxiliary request would have led to a totally new discussion of the facts. Thus, exercising its discretion in accordance with the established practice of the boards of appeal, the board did not admit the second auxiliary request into the proceedings.

Additionally, the board refers to Article 10b(1) of the Rules of Procedure of the Boards of Appeal, OJ EPO 2003, 64, in force from 1 May 2003,

OJ EPO 2003, 61, and applying to all appeals filed after that date, OJ EPO 2003, 67.

The appeal in suit was filed on 28 August 2003.

4. As far as novelty of the claimed subject-matter of the main request is concerned, the board has no reason to depart from the conclusion of the examining division in the impugned decision.

The subject-matter of the auxiliary request is further restricted and therefore meets the requirements of Article 54 EPC as well.

5. *Inventive step*

- 5.1 The subject-matter of the main request concerns "A pharmaceutical composition which comprises an alkanoyl L-carnitine and a statin".

- 5.2 Document (1), an abstract of a scientific article in a journal, represents the closest state of the art.

According to its text, this abstract relates to the use of L-carnitine and simvastatin, as monotherapies and simultaneously administered. A synergistic normolipidemic effect of the two compounds in the treatment of altered lipidemia is shown. In this document L-carnitine is not esterified.

- 5.3 In the absence of any comparative study with respect to (1) as closest state of the art, the technical problem underlying the application in suit can only be seen in the provision of a further pharmaceutical composition.

- 5.4 The solution to this problem is the provision of a pharmaceutical composition exhibiting the features of claim 1 of the main request.
- 5.5 Having regard to the "clinical study" set out in the application in suit (see pages 7 to 11 of the application as filed), the board is convinced that the problem has been plausibly solved. The normolipidemic effect, an anticholesterolaemic and antitriglyceridaemic action, is credible.
- 5.6 However, in order to supply another pharmaceutical composition, with respect to the co-administration of L-carnitine and simvastatin (see document (1)), the skilled person would take into account the teaching of document (3).

He would know from (3) that "in contrast to findings ... where the level of triglycerides and free fatty acids were not affected by carnitine per se, it has been found that a decrease in triglycerides and free fatty acids occurs upon the administration of acetylcarnitine" (see column 2, lines 21 to 25). Additionally, the teaching of (3) shows that in a hypercholesterolemic diet fed rat, administration of 200 mg/kg of L-acetylcarnitine or D,L-acetylcarnitine effected a reduction in serum total lipids and triglycerides (see column 2, lines 62 to 66). This effect of preventing or minimizing conditions which lead to infarction cardiac ischemia ..., namely a high level of cholesterols and triglycerides in the plasma, is attributed to acylcarnitines, comprising *inter alia* acetyl- and propionylcarnitine (see (3), column 1,

line 67, to column 2, line 2, together with column 2, lines 3 to 7, and column 1, lines 57 to 67).

Thus, the person skilled in the art knows that the use of acylated carnitine instead of carnitine will achieve some or even a better reduction of serum total lipids and triglycerides, meaning the same as a normolipidemic effect or the anticholesterolaemic and antitriglyceridaemic action as exhibited in the application in suit.

Trying to find a pharmaceutical composition exhibiting another or even an improved normolipidemic action with respect to a mixture of L-carnitine and simvastatin, he will take into account the teaching of (3) and accordingly is led to the use of acylated L-carnitine together with simvastatin.

5.7 Consequently, the board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step.

5.8 The same holds for the subject-matter of the first auxiliary request, since the use of propionyl carnitine as an acylcarnitine is particularly mentioned in (3), column 1, lines 58 to 64, and thus the reasoning according to the subject-matter of the main request applies *mutatis mutandis*.

6. *Arguments of the appellant*

6.1 With reference to the wording in the application as filed, "the use of lower doses of statins as compared to the routine doses (10-40 mg/day) makes the

co-ordinated use as per the invention particularly useful and safe" (page 7, line 15, together with page 4, lines 19 to 21), the appellant claims as the problem to be solved the reduction of the daily dosage of simvastatin in a pharmaceutical exhibiting anticholesterolaemic and antitriglyceridaemic action.

This approach, however, refers to the sole administration of only one component of the two component composition already known from the state of the art and not to its co-administration with the second component. Therefore, it cannot substitute for a comparative study using the mixture of L-carnitine and simvastatin, known from (1) on the one hand and acylated L-carnitine and simvastatin on the other.

- 6.2 Additionally, the assumption of a dose of at least 10 mg/day of a statin, particularly simvastatin, to be a routine dose is a mere allegation without any evidence.

Apart from the statement of this allegation, such a dosage of 10 mg/day of simvastatin is only mentioned in the "clinical study" comprised in the application as filed. It is used to establish comparative values of triglyceride (see page 9, lines 18 to 19) and cholesterolaemia (see page 10, lines 9 to 14). In this context, the dosage of 10 mg/day of simvastatin seems to be arbitrarily chosen for the purpose of comparison (page 7, line 12, of the application as filed) and there is no general relevance at all in the sense of a routine dose. Particularly it is not a routine dose for the co-administration of L-carnitine and simvastatin together.

Since such a routine dose is not mentioned in any of the other documents on file, there is no evidence in support of the statement that 10-40 mg/day of simvastatin inevitably were routine doses in the necessary context. Thus, the value of the advantage achieved by means of the teaching of the application in suit is based on a mere statement of the applicant and not on any experiment or other evidence from the state of the art.

Accordingly, the problem underlying the application in suit cannot be to provide for an improved pharmaceutical composition exhibiting its anticholesterolaemic and antitriglyceridaemic effect by means of a reduced dose of statin (see page 4 of the application as filed, lines 8 to 13).

- 6.3 Finally, the applicant argued that the skilled person was prevented from taking into account document (3) because there the racemic D,L-derivatives of carnitine instead of L-carnitine were used and because an increase in the level of high density lipoprotein (HDL) was stated.

However, the increase of HDL and the subsequent contribution to the correction of the imbalance of the ratio of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) vis-à-vis HDL, (see (3), column 2, lines 25 to 49) was not the single beneficial effect of the use of acylcarnitines reported in (3). The total effect, i.e. "preventing or minimizing conditions which lead to infarction cardiac ischemia ...", is matched by a significant reduction of

serum total lipids and triglycerides, namely both LDL and VLDL, and by an increase in the level of HDL, correcting the imbalance of lipoproteins *in summa* (see column 2, line 63, to column 3, line 3).

Thus, the skilled person had to expect an improved anticholesterolaemic and antitriglyceridaemic effect from the use of acylcarnitines instead of carnitine.

This must also be true for the substitution of the enantiomer L-carnitine by L-acylcarnitine, since in document (3), table 1, parallel experiments are set out for the use of racemic D,L-acetylcarnitine and for the use of the enantiomer L-acetylcarnitine, both used as model substances for acylcarnitines in general (including L-propionylcarnitine).

Consequently, in these circumstances the arguments of the appellant cannot succeed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Townend

U. Oswald